PCT

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jeannine CHOPPIN et al. CONFIRMATION NO. 5483

Serial No. 09/980,523
(PCT/FR00/01513)

#5

Filed December 3, 2001

POLYEPITOPIC PROTEIN FRAGMENTS OF THE E6 AND E7 PROTEINS OF HPV, THEIR PRODUCTION AND THEIR USE PARTICULARLY IN VACCINATION

AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Responsive to the Official Action of February 27, 2002, please amend the above-identified application as follows:

IN THE SPECIFICATION:

A substitute specification is submitted herewith.

IN THE CLAIMS:

Amend claim 5 as follows:

5. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 30 amino acids delimited by the amino acids located in positions 15 and 44 of the peptide sequence of the E6 protein of HPV, and characterized by the peptide sequence SEQ ID NO: 4 as follows:

(15)RPRKLPQLCTELQTTIHDIILECVYCKQQL(44)

said fragment containing 9 epitopes binding stably to at

least one of the 8 HLA molecules of the following types: A2, A11, A29, B7, B8, B35, B44, or B51, said epitopes being the following:

-(15)RPRKLPQL(22) (residues 15 to 22 of SEQ ID NO: 2) binding stably to HLA molecules of the B7 or B35 type,

-(18)KLPQLCTEL(26) (residues 18 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(19)LPQLCTEL(26) (residues 19 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the B51 type,

-(21)QLCTELQTTI(30) (residues 21 to 30 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(24)TELQTTIHDI(33) (residues 24 to 33 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(29)TIHDIILRCV(38) (residues 29 to 38 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(33)IILECVYCK(41) (residues 33 to 41 of SEQ ID NO: 2) binding stably to HLA molecules of the A11 type,

-(35)LECVYCKQQL(44) (residues 35 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(37)CVYCKQQL(44) (residues 37 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type.

Amend claim 6 as follows:

6. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 46 and 62, or to the fragment of 22 amino acids delimited by the amino acids located in positions 46 and 67 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 6 as follows:

(46)RREVYDFAFRDLCIVYRDGNPY(67)

said fragment containing 6 epitopes binding stably to at

least one of the 10 HLA molecules of the following types: A2, A3, A11, A24, A29, B7, B27, B35, B44, or B51, said epitopes being the following:

-(46)RREVYDFAFR(55) (residues 46 to 55 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) (residues 49 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) (residues 50 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) (residues 52 to 60 of SEQ ID NO: 2) binding stably to HLA molecules of the A2, B35, B51, or B7 type,

-(54)FRDLCIVYR(62) (residues 54 to 62 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(59)IVYRDGNPY(67) (residues 59 to 67 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type.

Amend claim 7 as follows:

7. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 29 amino acids delimited by the amino acids located in positions 80 and 108 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 8 as follows:

(80)ISEYRHYCYSLYGTTLEQQYNKPLCDLLI(108)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A1, A3, A11, A24, A29, B7, B18, B35, B44, or B51, said epitopes being the following:

-(80)ISEYRHYCY(88) (residues 80 to 88 of SEQ ID NO: 2) binding stably to HLA molecules of the A1 or B18 type,

-(81)SEYRHYCY(88) (residues 81 to 88 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(87)CYSLYGTTL(95) (residues 87 to 95 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(94)TLEQQYNK(101) (residues 94 to 101 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(95)LEQQYNKPL(103) (residues 95 to 103 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(101)KPLCDLLI(108) (residues 101 to 108 of SEQ ID NO: 2) binding stably to HLA molecules of the B7, B35 or B51 type.

Amend claim 8 as follows:

8. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 22 amino acids delimited by the amino acids located in positions 118 and 139 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 10 as follows:

(118)CPEEKQRHLDKKQRFHNIRGRW(139)

said fragment containing 6 epitopes binding stably to at least one of the 7 HLA molecules of the following types: A24, B8, B18, B27, B35, B44, or B51, said epitopes being the following:

-(118)CPEEKQRHL(126) (residues 118 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B8, B18, B35, B51 type,

-(119)PEEKQRHL(126) (residues 119 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B44 type,

-(127)DKKQRFHNI(135) (residues 127 to 135 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,

-(128)KKQRFHNIR(136) (residues 128 to 136 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(130)QRFHNIRGRW(139) (residues 130 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(131)RFHNIRGRW(139) (residues 131 to 139 of SEQ ID NO: 2)

binding stably to HLA molecules of the A24 type.

Amend claim 11 as follows:

11. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 23 amino acids delimited by the amino acids located in positions 3 and 25 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 14 as follows:

(3)GDTPTLHEYMLDLQPETTDLYCY(25)

said fragment containing 5 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A2, B18, B35, B44 or B62, said epitopes being the following:

-(3)GDTPTLHEY(11) (residues 3 to 11 of SEQ ID NO: 12) binding stably to HLA molecules of the B44 type,

-(5)TPTLHEYML(13) (residues 5 to 13 of SEQ ID NO: 12) binding stably to HLA molecules of the B35 type,

-(11)YMLDLQPETT(20) (residues 11 to 20 of SEQ ID NO: 12) binding stably to HLA molecules of the A2 type,

-(15)LQPETTDLY(23) (residues 15 to 23 of SEQ ID NO: 12) binding stably to HLA molecules of the B62 type,

-(16)QPETTDLYCY(25) (residues 16 to 25 of SEQ ID NO: 12) binding stably to HLA molecules of the A1 or B18 type.

Amend claim 12 as follows:

12. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 44 and 60 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 16 as follows:

(44)QAEPDRAHYNIVTFCCK(60)

said fragment containing 4 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A3, A11, A29, B7, B18, B35, or B44, said epitopes being the following:

-(44)QAEPDRAHY(52) (residues 44 to 52 of SEQ ID NO: 12) binding stably to HLA molecules of the A1 or B18 type,

-(45)AEPDRAHY(52) (residues 45 to 52 of SEQ ID NO: 12) binding stably to HLA molecules of the A29 or B44 type,

-(46)EPDRAHYNIV(55) (residues 46 to 55 of SEQ ID NO: 12) binding stably to HLA molecules of the B7 or B35 type,

-(53)NIVTFCCK(60) (residues 53 to 60 of SEQ ID NO: 12) binding stably to HLA molecules of the A3 or A11 type.

Amend claim 13 as follows:

13. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 19 amino acids delimited by the amino acids located in positions 79 and 97 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 18 as follows:

(79)LEDLLMGTLGIVCPICSQK(97)

said fragment containing 4 epitopes binding stably to at least one of the 5 HLA molecules of the following types: A2, A3, A11, A29 or B44, said epitopes being the following:

-(79)LEDLLMGTL(87) (residues 79 to 87 of SEQ ID NO: 12) binding stably to HLA molecules of the A29 or B44 type,

-(82)LLMGTLGIV(90) (residues 82 to 90 of SEQ ID NO: 12)binding stably to HLA molecules of the A2 type,

-(86)TLGIVCPI(93) (residues 86 to 93 of SEQ ID NO: 12) binding stably to HLA molecules of the A2 type,

-(89)IVCPICSQK(97) (residues 89 to 97 of SEQ ID NO: 12)binding stably to HLA molecules of the A3 or A11 type.

Amend claim 21 as follows:

21. (amended) Epitopes of the E6 protein of HPV selected from the following:

-(19)LPQLCTEL(26) (residues 19 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the B51 type,

-(21)QLCTELQTTI(30) (residues 21 to 30 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(24)TELQTTIHDI(33) (residues 24 to 33 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(33)IILECVYCK(41) (residues 33 to 41 of SEQ ID NO: 2) binding stably to HLA molecules of the A11 type,

-(35)LECVYCKQQL(44) (residues 35 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(37)CVYCKQQL(44) (residues 37 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,

-(46)RREVYDFAFR(55) (residues 46 to 55 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) (residues 49 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) (residues 50 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) (residues 52 to 60 of SEQ ID NO: 2) binding stably to HLA molecules of the A2, B35, B51, or B7 type,

-(54)FRDLCIVYR(62) (residues 54 to 62 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(59)IVYRDGNPY(67) (residues 59 to 67 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(81)SEYRHYCY(88) (residues 81 to 88 of SEQ ID NO: 2)binding stably to HLA molecules of the A29 or B44 type,

-(87)CYSLYGTTL(95) (residues 87 to 95 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(94)TLEQQYNK(101) (residues 94 to 101 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(95)LEQQYNKPL(103) (residues 95 to 103 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,
-(101)KPLCDLLI(108) (residues 101 to 108 of SEQ ID NO: 2)binding stably to HLA molecules of the B7, B35 or B51 type,
-(118)CPEEKQRHL(126) (residues 118 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B8, B18, B35, B51 type,

-(119)PEEKQRHL(126) (residues 119 to 126 of SEQ ID NO: 2)binding stably to HLA molecules of the B44 type,
-(127)DKKQRFHNI(135) (residues 127 to 135 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,
-(128)KKQRFHNIR(136) (residues 128 to 136 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(130)QRFHNIRGRW(139) (residues 130 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(131)RFHNIRGRW(139) (residues 131 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type.

Amend claim 22 as follows:

22. (amended) Epitopes of the E7 protein of HPV selected from the following:
-(3)GDTPTLHEY(11) (residues 3 to 11 of SEQ ID NO: 12) binding stably to HLA molecules of the B44 type,
-(5)TPTLHEYML(13) (residues 5 to 13 of SEQ ID NO: 12) binding stably to HLA molecules of the B35 type,
-(15)LQPETTDLY(23) (residues 15 to 23 of SEQ ID NO: 12) binding stably to HLA molecules of the B62 type,
-(16)QPETTDLYCY(25) (residues 16 to 25 of SEQ ID NO: 12) binding stably to HLA molecules of the A1 or B18 type,
-(45)AEPDRAHY(52) (residues 45 to 52 of SEQ ID NO: 12) binding stably to HLA molecules of the A29, B44 type,
-(46)EPDRAHYNIV(55) (residues 46 to 55 of SEQ ID NO: 12) binding stably to HLA molecules of the B7 or B35 type,
-(53)NIVTFCCK(60) (residues 53 to 60 of SEQ ID NO:

12)binding stably to HLA molecules of the A3, A11 type,
-(79)LEDLLMGTL(87) (residues 79 to 87 of SEQ ID NO: 12) binding stably to HLA molecules of the A29, B44 type,
-(89)IVCPICSQK(97) (residues 89 to 97 of SEQ ID NO: 12) binding stably to HLA molecules of the A3, A11 type.

REMARKS

Responsive to the requirement for submission of a Sequence Listing, imposed in the outstanding Official Action, the same is provided herewith, attached to the present amendment, in paper and disk formats. Applicants hereby state that the attached paper and computer-readable copies have the same content and introduce no new matter into the present application.

In this regard, the specification and claims have been amended so that they are commensurate with the submission of the present Sequence Listing.

A substitute specification is provided, together with a marked-up copy of the changes made to the specification. The revised specification contains no new matter.

In view of the above, it is respectfully submitted that the above-identified application complies with the requirements of patent applications containing nucleotide sequences and/or amino acid sequence disclosures.

The outstanding Official Action also required the submission of an oath or declaration of the inventors. As such, a declaration of the inventors is provided with the present amendment.

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Attached hereto is a marked-up version of the changes made to the claims. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

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April 29, 2002

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 5 has been amended as follows:

5. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 30 amino acids delimited by the amino acids located in positions 15 and 44 of the peptide sequence of the E6 protein of HPV, and characterized by the peptide sequence SEQ ID NO: 4 as follows:

(15)RPRKLPQLCTELQTTIHDIILECVYCKQQL(44)

said fragment containing 9 epitopes binding stably to at least one of the 8 HLA molecules of the following types: A2, A11, A29, B7, B8, B35, B44, or B51, said epitopes being the following:

-(15)RPRKLPQL(22) (residues 15 to 22 of SEQ ID NO: 2) binding stably to HLA molecules of the B7 or B35 type,

-(18)KLPQLCTEL(26) (residues 18 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(19)LPQLCTEL(26) (residues 19 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the B51 type,

-(21)QLCTELQTTI(30) (residues 21 to 30 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(24)TELQTTIHDI(33) (residues 24 to 33 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(29)TIHDIILRCV(38) (residues 29 to 38 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(33)IILECVYCK(41) (residues 33 to 41 of SEQ ID NO: 2) binding stably to HLA molecules of the A11 type,

-(35)LECVYCKQQL(44) (residues 35 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(37)CVYCKQQL(44) (residues 37 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type.

Claim 6 has been amended as follows:

6. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 46 and 62, or to the fragment of 22 amino acids delimited by the amino acids located in positions 46 and 67 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 6 as follows:

(46)RREVYDFAFRDLCIVYRDGNPY(67)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A2, A3, A11, A24, A29, B7, B27, B35, B44, or B51, said epitopes being the following:

-(46)RREVYDFAFR(55) (residues 46 to 55 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) (residues 49 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) (residues 50 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) (residues 52 to 60 of SEQ ID NO: 2) binding stably to HLA molecules of the A2, B35, B51, or B7 type,

-(54)FRDLCIVYR(62) (residues 54 to 62 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(59)IVYRDGNPY(67) (residues 59 to 67 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type.

Claim 7 has been amended as follows:

7. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 29 amino acids delimited by the amino acids located in positions 80 and 108 of the peptide sequence of the E6 protein of HPV, this latter

fragment being characterized by the peptide sequence SEQ ID NO: 8 as follows:

(80)ISEYRHYCYSLYGTTLEQQYNKPLCDLLI(108)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A1, A3, A11, A24, A29, B7, B18, B35, B44, or B51, said epitopes being the following:

-(80)ISEYRHYCY(88) (residues 80 to 88 of SEQ ID NO: 2) binding stably to HLA molecules of the A1 or B18 type,

-(81)SEYRHYCY(88) (residues 81 to 88 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(87)CYSLYGTTL(95) (residues 87 to 95 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(94)TLEQQYNK(101) (residues 94 to 101 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,

-(95)LEQQYNKPL(103) (residues 95 to 103 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(101)KPLCDLLI(108) (residues 101 to 108 of SEQ ID NO: 2) binding stably to HLA molecules of the B7, B35 or B51 type.

Claim 8 has been amended as follows:

8. (twice amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 22 amino acids delimited by the amino acids located in positions 118 and 139 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 10 as follows:

(118)CPEEKQRHLDKKQRFHNIRGRW(139)

said fragment containing 6 epitopes binding stably to at least one of the 7 HLA molecules of the following types: A24, B8, B18, B27, B35, B44, or B51, said epitopes being the following:

-(118)CPEEKQRHL(126) (residues 118 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B8, B18, B35, B51 type,
-(119)PEEKQRHL(126) (residues 119 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B44 type,
-(127)DKKQRFHNI(135) (residues 127 to 135 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,
-(128)KKQRFHNIR(136) (residues 128 to 136 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(130)QRFHNIRGRW(139) (residues 130 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(131)RFHNIRGRW(139) (residues 131 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type.

Claim 11 has been amended as follows:

11. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 23 amino acids delimited by the amino acids located in positions 3 and 25 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 14 as follows:

(3)GDTPTLHEYMLDLQPETTDLYCY(25)

said fragment containing 5 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A2, B18, B35, B44 or B62, said epitopes being the following:

-(3)GDTPTLHEY(11) (residues 3 to 11 of SEQ ID NO: 12) binding stably to HLA molecules of the B44 type,

-(5)TPTLHEYML(13) (residues 5 to 13 of SEQ ID NO: 12) binding stably to HLA molecules of the B35 type,

-(11)YMLDLQPETT(20) (residues 11 to 20 of SEQ ID NO: 12) binding stably to HLA molecules of the A2 type,

-(15)LQPETTDLY(23) (residues 15 to 23 of SEQ ID NO: 12) binding stably to HLA molecules of the B62 type,

-(16)QPETTDLYCY(25) (residues 16 to 25 of SEQ ID NO: 12)

binding stably to HLA molecules of the A1 or B18 type.

Claim 12 has been amended as follows:

12. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 44 and 60 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 16 as follows:

(44)QAEPDRAHYNIVTFCCK(60)

said fragment containing 4 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A3, A11, A29, B7, B18, B35, or B44, said epitopes being the following:

-(44)QAEPDRAHY(52) (residues 44 to 52 of SEQ ID NO: 12) binding stably to HLA molecules of the A1 or B18 type,

-(45)AEPDRAHY(52) (residues 45 to 52 of SEQ ID NO: 12) binding stably to HLA molecules of the A29 or B44 type,

-(46)EPDRAHYNIV(55) (residues 46 to 55 of SEQ ID NO: 12) binding stably to HLA molecules of the B7 or B35 type,

-(53)NIVTFCCK(60) (residues 53 to 60 of SEQ ID NO: 12) binding stably to HLA molecules of the A3 or A11 type.

Claim 13 has been amended as follows:

13. (twice amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 19 amino acids delimited by the amino acids located in positions 79 and 97 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 18 as follows:

(79)LEDLLMGTLGIVCPICSQK(97)

said fragment containing 4 epitopes binding stably to at

least one of the 5 HLA molecules of the following types: A2, A3, A11, A29 or B44, said epitopes being the following:

-(79)LEDLLMGTL(87) (residues 79 to 87 of SEQ ID NO: 12) binding stably to HLA molecules of the A29 or B44 type,

-(82)LLMGTLGIV(90) (residues 82 to 90 of SEQ ID NO: 12) binding stably to HLA molecules of the A2 type,

-(86)TLGIVCPI(93) (residues 86 to 93 of SEQ ID NO: 12) binding stably to HLA molecules of the A2 type,

-(89)IVCPICSQK(97) (residues 89 to 97 of SEQ ID NO: 12) binding stably to HLA molecules of the A3 or A11 type.

Claim 21 has been amended as follows:

21. (amended) Epitopes of the E6 protein of HPV selected from the following:

-(19)LPQLCTEL(26) (residues 19 to 26 of SEQ ID NO: 2) binding stably to HLA molecules of the B51 type,

-(21)QLCTELQTTI(30) (residues 21 to 30 of SEQ ID NO: 2) binding stably to HLA molecules of the A2 type,

-(24)TELQTTIHDI(33) (residues 24 to 33 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(33)IILECVYCK(41) (residues 33 to 41 of SEQ ID NO: 2) binding stably to HLA molecules of the A11 type,

-(35)LECVYCKQQL(44) (residues 35 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(37)CVYCKQQL(44) (residues 37 to 44 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,

-(46)RREVYDFAFR(55) (residues 46 to 55 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) (residues 49 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) (residues 50 to 57 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) (residues 52 to 60 of SEQ ID NO: 2) binding stably to HLA molecules of the A2, B35, B51, or B7

type,
-(54)FRDLCIVYR(62) (residues 54 to 62 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,
-(59)IVYRDGNPY(67) (residues 59 to 67 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,
-(81)SEYRHYCY(88) (residues 81 to 88 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,
-(87)CYSLYGTTL(95) (residues 87 to 95 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type,
-(94)TLEQQYNK(101) (residues 94 to 101 of SEQ ID NO: 2) binding stably to HLA molecules of the A3 or A11 type,
-(95)LEQQYNKPL(103) (residues 95 to 103 of SEQ ID NO: 2) binding stably to HLA molecules of the A29 or B44 type,
-(101)KPLCDLLI(108) (residues 101 to 108 of SEQ ID NO: 2) binding stably to HLA molecules of the B7, B35 or B51 type,
-(118)CPEEKQRHL(126) (residues 118 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B8, B18, B35, B51 type,
-(119)PEEKQRHL(126) (residues 119 to 126 of SEQ ID NO: 2) binding stably to HLA molecules of the B44 type,
-(127)DKKQRFHNI(135) (residues 127 to 135 of SEQ ID NO: 2) binding stably to HLA molecules of the B8 type,
-(128)KKQRFHNIR(136) (residues 128 to 136 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(130)QRFHNIRGRW(139) (residues 130 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the B27 type,
-(131)RFHNIRGRW(139) (residues 131 to 139 of SEQ ID NO: 2) binding stably to HLA molecules of the A24 type.

Claim 22 has been amended as follows:

22. (amended) Epitopes of the E7 protein of HPV selected from the following:
-(3)GDTPTLHEY(11) (residues 3 to 11 of SEQ ID NO: 12) binding stably to HLA molecules of the B44 type,
-(5)TPTLHEYML(13) (residues 5 to 13 of SEQ ID NO: 12)

binding stably to HLA molecules of the B35 type,
-(15)LQPETTDLY(23) (residues 15 to 23 of SEQ ID NO: 12)
binding stably to HLA molecules of the B62 type,
-(16)QPETTDLYCY(25) (residues 16 to 25 of SEQ ID NO: 12)
binding stably to HLA molecules of the A1 or B18 type,
-(45)AEPDRAHY(52) (residues 45 to 52 of SEQ ID NO: 12)
binding stably to HLA molecules of the A29, B44 type,
-(46)EPDRAHYNIV(55) (residues 46 to 55 of SEQ ID NO: 12)
binding stably to HLA molecules of the B7 or B35 type,
-(53)NIVTFCCK(60) (residues 53 to 60 of SEQ ID NO: 12)
binding stably to HLA molecules of the A3, A11 type,
-(79)LEDLLMGTL(87) (residues 79 to 87 of SEQ ID NO: 12)
binding stably to HLA molecules of the A29, B44 type,
-(89)IVCPICSQK(97) (residues 89 to 97 of SEQ ID NO: 12)
binding stably to HLA molecules of the A3, A11 type.

PATENTS

PATENTS

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Jeannine CHOPPIN et al. Box PCT

Serial No. (unknown) (PCT/FR00/01513) Application Branch

Filed herewith

POLYEPITOPIC PROTEIN FRAGMENTS OF THE E6 AND E7 PROTEINS OF HPV, THEIR PRODUCTION AND THEIR USE PARTICULARLY IN VACCINATION

PRELIMINARY AMENDMENT

Commissioner for Patents

Washington, D.C. 20231

Sir:

Prior to the first Official Action and calculation of the filing fee, please amend the above-identified application as follows:

IN THE CLAIMS:

Claims 3-9, and 11-20 have been amended as follows:

--3. (amended) Polyepitopic fragments of the E6 protein of HPV according to claim 1, characterized in that they comprise a peptide sequence of about 15 to 30 amino acids, this peptide sequence containing amino acid sequences of at least 5 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the proteasome, such that at least 6

HLA molecules of different types bind to these epitopes, these 6 HLA molecules being selected from those of types A1, A2, A3, A11, A24, A29, B7, B8, B18, B27, B35, B44 and B51.--

--4. (amended) Polyepitopic fragments of the E6 protein of HPV according to claim 1, characterized in that they all comprise an epitope binding to the HLA molecule of type B35, an epitope binding to the HLA molecule of type B44, and an epitope binding to the HLA molecule of type B51.--

--5. (amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 30 amino acids delimited by the amino acids located in positions 15 and 44 of the peptide sequence of the E6 protein of HPV, and characterized by the peptide sequence SEQ ID NO: 4 as follows:

(15)RPRKLPQLCTELQTTIHDIILECVYCKQQL(44)

said fragment containing 9 epitopes binding stably to at least one of the 8 HLA molecules of the following types: A2, A11, A29, B7, B8, B35, B44, or B51, said epitopes being the following:

- (15)RPRKLPQL(22) binding stably to HLA molecules of the B7 or B35 type,
- (18)KLPQLCTEL(26) binding stably to HLA molecules of the A2 type,

-(19)LPQLCTEL(26) binding stably to HLA molecules of the B51 type,

-(21)QLCTELQTTI(30) binding stably to HLA molecules of the A2 type,

-(24)TELQTTIHDI(33) binding stably to HLA molecules of the A29 or B44 type,

-(29)TIHDIILRCV(38) binding stably to HLA molecules of the A2 type,

-(33)IILECVYCK(41) binding stably to HLA molecules of the A11 type,

-(35)LECVYCKQQL(44) binding stably to HLA molecules of the A29 or B44 type,

-(37)CVYCKQQL(44) binding stably to HLA molecules of the B8 type.--

--6. (amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 46 and 62, or to the fragment of 22 amino acids delimited by the amino acids located in positions 46 and 67 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 6 as follows:

(46)RREVYDFAFRDLCIVYRDGNPY(67)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following

types: A2, A3, A11, A24, A29, B7, B27, B35, B44, or B51, said epitopes being the following:

-(46)RREVYDFAFR(55) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) binding stably to HLA molecules of the A2, B35, B51, or B7 type,

-(54)FRDLCIVYR(62) binding stably to HLA molecules of the A3 or A11 type,

-(59)IVYRDGNPY(67) binding stably to HLA molecules of the A3 or A11 type.--

--7. (amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 29 amino acids delimited by the amino acids located in positions 80 and 108 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 8 as follows:

(80)ISEYRHYCYSLYGTTLEQQYNKPLCDLLI(108)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A1, A3, A11, A24, A29, B7, B18, B35, B44, or B51, said epitopes being the following:

-(80)ISEYRHYCY(88) binding stably to HLA molecules of the A1 or B18 type,

-(81)SEYRHYCY(88) binding stably to HLA molecules of the A29 or B44 type,

-(87)CYSLYGTTL(95) binding stably to HLA molecules of the A24 type,

-(94)TLEQQYNK(101) binding stably to HLA molecules of the A3 or A11 type,

-(95)LEQQYNKPL(103) binding stably to HLA molecules of the A29 or B44 type,

-(101)KPLCDLLI(108) binding stably to HLA molecules of the B7, B35 or B51 type.--

--8. (amended) Polyepitopic fragment of the E6 protein of HPV according to claim 1, characterized in that it corresponds to the fragment of 22 amino acids delimited by the amino acids located in positions 118 and 139 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 10 as follows:

(118)CPEEKQRHLDKKQRFHNIRGRW(139)

said fragment containing 6 epitopes binding stably to at least one of the 7 HLA molecules of the following types: A24, B8, B18, B27, B35, B44, or B51, said epitopes being the following:

-(118)CPEEKQRHL(126) binding stably to HLA molecules of the B8, B18, B35, B51 type,

-(119)PEEKQRHL(126) binding stably to HLA molecules of the B44 type,

-(127)DKKQRFHNI(135) binding stably to HLA molecules of the B8 type,

-(128)KKQRFHNIR(136) binding stably to HLA molecules of the B27 type,

-(130)QRFHNIRGRW(139) binding stably to HLA molecules of the B27 type,

-(131)RFHNIRGRW(139) binding stably to HLA molecules of the A24 type.--

--9. (amended) Polyepitopic fragments of the E7 protein of HPV according to claim 1, characterized in that they comprise a peptide sequence of about 15 to 30 amino acids, this peptide sequence containing amino acid sequences of at least 3 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the proteasome, such that at least 4 HLA molecules of different types bind to these epitopes, these 4 HLA molecules being selected from those of type A1, A2, A3, A11, A29, B7, B18, B35, B44 and B62.--

--11. (amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 23 amino acids delimited by the

amino acids located in positions 3 and 25 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 14 as follows:

(3)GDTPTLHEYMLDLQPETTDLYCY(25)

said fragment containing 5 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A2, B18, B35, B44 or B62, said epitopes being the following:

-(3)GDTPTLHEY(11) binding stably to HLA molecules of the B44 type,

-(5)TPTLHEYML(13) binding stably to HLA molecules of the B35 type,

-(11)YMLDLQPETT(20) binding stably to HLA molecules of the A2 type,

-(15)LQPETTDLY(23) binding stably to HLA molecules of the B62 type,

-(16)QPETTDLYCY(25) binding stably to HLA molecules of the A1 or B18 type.--

--12. (amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 44 and 60 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 16 as follows:

(44)QAEPDRAHYNIVTFCCK(60)

said fragment containing 4 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A3, A11, A29, B7, B18, B35, or B44, said epitopes being the following:

-(44)QAEPDRAHY(52) binding stably to HLA molecules of the A1 or B18 type,

-(45)AEPDRAHY(52) binding stably to HLA molecules of the A29 or B44 type,

-(46)EPDRAHYNIV(55) binding stably to HLA molecules of the B7 or B35 type,

-(53)NIVTFCCK(60) binding stably to HLA molecules of the A3 or A11 type.--

--13. (amended) Polyepitopic fragment of the E7 protein of HPV according to claim 9, characterized in that it corresponds to the fragment of 19 amino acids delimited by the amino acids located in positions 79 and 97 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 18 as follows:

(79)LEDLLMGTLGIVCPICSQK(97)

said fragment containing 4 epitopes binding stably to at least one of the 5 HLA molecules of the following types: A2, A3, A11, A29 or B44, said epitopes being the following:

-(79)LEDLLMGTL(87) binding stably to HLA molecules of the A29 or B44 type,

-(82)LLMGTLGIV(90) binding stably to HLA molecules of the A2 type,

-(86)TLGIVCPI(93) binding stably to HLA molecules of the A2 type,

-(89)IVCPICSQK(97) binding stably to HLA molecules of the A3 or A11 type.--

--14. (amended) Polyepitopic fragments of the E6 or E7 protein according to claim 1, characterized in that they correspond to the peptide sequences derived from the polyepitopic fragments defined in claim 1, particularly:

- by substitution, and/or suppression, and/or addition of one or several amino acids, of the above-mentioned fragments, and/or

- by modification of at least one -CO-NH- peptide linkage of the peptide chain of the above-mentioned fragments, particularly by introduction of a retro or retro-inverso type linkage, and/or

- by substitution of at least one amino acid of the peptide chain of the sequence or of the above-mentioned fragment, with a non-proteinogenic amino acid,

said derived sequences containing peptides or pseudopeptides binding specifically to the same molecule or molecules of MCH as those binding to the peptides contained in the above-mentioned polyepitopic fragments from which they derive.--

--15. (amended) Nucleotide sequences coding for a polyepitopic fragment or for a peptide sequence derived according to claim 1, said nucleotide sequences being derived from the sequence SEQ ID NO: 1 coding for the E6 protein, or from the sequence SEQ ID NO: 11 coding for the E7 protein.--

--16. (amended) Nucleotide sequences according to claim 15, selected from the following:

- the sequence SEQ ID NO: 3, coding for the polyepitopic fragment SEQ ID NO: 4,
- the sequence SEQ ID NO: 5, coding for the polyepitopic fragment SEQ ID NO: 6,
- the sequence SEQ ID NO: 7, coding for the polyepitopic fragment SEQ ID NO: 8,
- the sequence SEQ ID NO: 9, coding for the polyepitopic fragment SEQ ID NO: 10,
- the sequence SEQ ID NO: 13, coding for the polyepitopic fragment SEQ ID NO: 14,
- the sequence SEQ ID NO: 15, coding for the polyepitopic fragment SEQ ID NO: 16,
- the sequence SEQ ID NO: 17, coding for the polyepitopic fragment SEQ ID NO: 18.--

--17. (amended) Polyclonal or monoclonal antibodies, directed against a polyepitopic fragment or against a peptide sequence derived according to claim 1.--

--18. (amended) Lipopeptide characterized in that it comprises:

- a peptide portion comprising one or several polyepitopic protein fragments, or a peptide sequence derived from said fragments, as defined in claim 1,

- and one or several lipophile portions, such as those comprising:

* a C4 to C20 hydrocarbon chain, saturated or unsaturated, linear or branched,

* or a steroid group, as the case may be bonded to the above-mentioned hydrocarbon chain,

said lipophilic portions being if desired associated with a short peptide vector comprising one or several ionized functions at physiological pH, and a function permitting the covalent bonding of said hydrocarbon chain and/or said steroid group.--

--19. (amended) Pharmaceutical composition, or vaccine, characterized in that it comprises:

- at least one polyepitopic fragment of the E6 or E7 protein of HPV, characterized in that they comprise a peptide sequence of about 15 to 30 amino acids, this peptide sequence containing amino acid sequences of at least 3 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the proteasome, such that at least 4 HLA molecules of

different types bind to these epitopes, these 4 HLA molecules being selected from among those of types A1, A2, A3, A11, A24, A29, B7, B8, B18, B27, B35, B44, B51 and B62,

- and/or at least one peptide sequence derived from this fragment, as defined in claim 14,

in association with a physiologically acceptable vehicle,

said polyepitopic protein fragment and/or its derived sequence being, as the case may be, associated with one or several other exogenous epitopes recognized by auxiliary T cells, such as the peptide fragment delimited by the amino acids located in positions 830 and 846 of the peptide sequence of the tetanus toxin, hemagglutinin, or PADRE epitope.

--20. (amended) The use of polyepitopic fragments of the E6 or E7 protein defined in claim 1, for the preparation of a medication or vaccine adapted for the prevention or treatment of pathologies connected with the infection of individuals by human papillomavirus, such as cervical intraepithelial neoplasias (CIN), invasive cancer of the neck of the uterus, vulvar intraepithelial neoplasias (VIN).--

Add the following new claims:

--23. (new) Pharmaceutical composition, or vaccine, characterized in that it comprises:

- at least one nucleotide sequence according to claim 15, coding for an above-mentioned polyepitopic fragment of the E6 or E7 protein,

- and/or at least one nucleotide sequence coding for a peptide sequence derived from this fragment, as defined above,

- and/or at least one above-mentioned suitable vector, selected particularly from the viruses, containing at least one above-mentioned nucleotide sequence,

in association with a physiologically acceptable vehicle.

--24. (new) Pharmaceutical composition, or vaccine, characterized in that it comprises:

- antibodies according to claim 17, directed against a polyepitopic fragment of the E6 or E7 protein, and/or against a peptide sequence derived from these fragments, as defined above.--

R E M A R K S

The above changes in the claims merely place this national stage application in the same condition as it was during Chapter II of the international stage, with the multiple dependencies being removed.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

Respectfully submitted,

YOUNG & THOMPSON

By _____

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December 3, 2001

Jeannine CHOPPIN et al. - Docket No. WOB1 AO INS

VERSION WITH MARKINGS TO SHOW CHANGES MADE

Claims 3-9, and 11-20 have been amended as follows:

--3. (amended) Polyepitopic fragments of the E6 protein of HPV according to claim 1~~ or 2~~, characterized in that they comprise a peptide sequence of about 15 to 30 amino acids, this peptide sequence containing amino acid sequences of at least 5 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the proteasome, such that at least 6 HLA molecules of different types bind to these epitopes, these 6 HLA molecules being selected from those of types A1, A2, A3, A11, A24, A29, B7, B8, B18, B27, B35, B44 and B51.--

--4. (amended) Polyepitopic fragments of the E6 protein of HPV according to ~~one of claims~~claim 1~~ to 3~~, characterized in that they all comprise an epitope binding to the HLA molecule of type B35, an epitope binding to the HLA molecule of type B44, and an epitope binding to the HLA molecule of type B51.--

--5. (amended) Polyepitopic fragment of the E6 protein of HPV according to ~~one of claims~~claim 1~~ to 4~~, characterized in that it corresponds to the fragment of 30 amino acids delimited by the amino acids located in positions

15 and 44 of the peptide sequence of the E6 protein of HPV, and characterized by the peptide sequence SEQ ID NO: 4 as follows:

(15)RPRKLPQLCTELQTTIHDIILECVYCKQQL(44)

said fragment containing 9 epitopes binding stably to at least one of the 8 HLA molecules of the following types: A2, A11, A29, B7, B8, B35, B44, or B51, said epitopes being the following:

- (15)RPRKLPQL(22) binding stably to HLA molecules of the B7 or B35 type,
- (18)KLPQLCTEL(26) binding stably to HLA molecules of the A2 type,
- (19)LPQLCTEL(26) binding stably to HLA molecules of the B51 type,
- (21)QLCTELQTTI(30) binding stably to HLA molecules of the A2 type,
- (24)TELQTTIHDI(33) binding stably to HLA molecules of the A29 or B44 type,
- (29)TIHDIILRCV(38) binding stably to HLA molecules of the A2 type,
- (33)IILECVYCK(41) binding stably to HLA molecules of the A11 type,
- (35)LECVYCKQQL(44) binding stably to HLA molecules of the A29 or B44 type,
- (37)CVYCKQQL(44) binding stably to HLA molecules of the B8 type.--

--6. (amended) Polyepitopic fragment of the E6 protein of HPV according to ~~one of claims~~claim 1 ~~to 4~~, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 46 and 62, or to the fragment of 22 amino acids delimited by the amino acids located in positions 46 and 67 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 6 as follows:

(46)RREVYDFAFRDLCIVYRDGNPY(67)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A2, A3, A11, A24, A29, B7, B27, B35, B44, or B51, said epitopes being the following:

-(46)RREVYDFAFR(55) binding stably to HLA molecules of the B27 type,

-(49)VYDFAFRDL(57) binding stably to HLA molecules of the A24 type,

-(50)YDFAFRDL(57) binding stably to HLA molecules of the A29 or B44 type,

-(52)FAFRDLCIV(60) binding stably to HLA molecules of the A2, B35, B51, or B7 type,

-(54)FRDLCIVYR(62) binding stably to HLA molecules of the A3 or A11 type,

-(59)IVYRDGNPY(67) binding stably to HLA molecules of the A3 or A11 type.--

--7. (amended) Polyepitopic fragment of the E6 protein of HPV according to ~~one of claims~~claim 1~~ to 4~~, characterized in that it corresponds to the fragment of 29 amino acids delimited by the amino acids located in positions 80 and 108 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 8 as follows:

(80) ISEYRHYCYSLYGTTLEQQYNKPLCDLLI (108)

said fragment containing 6 epitopes binding stably to at least one of the 10 HLA molecules of the following types: A1, A3, A11, A24, A29, B7, B18, B35, B44, or B51, said epitopes being the following:

- (80) ISEYRHYCY (88) binding stably to HLA molecules of the A1 or B18 type,
- (81) SEYRHYCY (88) binding stably to HLA molecules of the A29 or B44 type,
- (87) CYSLYGTTL (95) binding stably to HLA molecules of the A24 type,
- (94) TLEQQYNK (101) binding stably to HLA molecules of the A3 or A11 type,
- (95) LEQQYNKPL (103) binding stably to HLA molecules of the A29 or B44 type,
- (101) KPLCDLLI (108) binding stably to HLA molecules of the B7, B35 or B51 type.--

--8. (amended) Polyepitopic fragment of the E6 protein of HPV according to ~~one of claims~~claim 1~~ to 4~~, characterized in that it corresponds to the fragment of 22 amino acids delimited by the amino acids located in positions 118 and 139 of the peptide sequence of the E6 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 10 as follows:

(118)CPEEKQRHLDKKQRFHNIRGRW(139)

said fragment containing 6 epitopes binding stably to at least one of the 7 HLA molecules of the following types: A24, B8, B18, B27, B35, B44, or B51, said epitopes being the following:

-(118)CPEEKQRHL(126) binding stably to HLA molecules of the B8, B18, B35, B51 type,

-(119)PEEKQRHL(126) binding stably to HLA molecules of the B44 type,

-(127)DKKQRFHNI(135) binding stably to HLA molecules of the B8 type,

-(128)KKQRFHNIR(136) binding stably to HLA molecules of the B27 type,

-(130)QRFHNIRGRW(139) binding stably to HLA molecules of the B27 type,

-(131)RFHNIRGRW(139) binding stably to HLA molecules of the A24 type.--

--9. (amended) Polyepitopic fragments of the E7 protein of HPV according to claim 1~~ or 2~~, characterized in

that they comprise a peptide sequence of about 15 to 30 amino acids, this peptide sequence containing amino acid sequences of at least 3 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the proteasome, such that at least 4 HLA molecules of different types bind to these epitopes, these 4 HLA molecules being selected from those of type A1, A2, A3, A11, A29, B7, B18, B35, B44 and B62.--

--11. (amended) Polyepitopic fragment of the E7 protein of HPV according to ~~one of claims~~claim 9 ~~or 10~~, characterized in that it corresponds to the fragment of 23 amino acids delimited by the amino acids located in positions 3 and 25 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 14 as follows:

(3)GDTPTLHEYMLDLQPETTDLYCY(25)

said fragment containing 5 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A2, B18, B35, B44 or B62, said epitopes being the following:

-(3)GDTPTLHEY(11) binding stably to HLA molecules of the B44 type,

-(5)TPTLHEYML(13) binding stably to HLA molecules of the B35 type,

-(11)YMLDLQPETT(20) binding stably to HLA molecules of the A2 type,

-(15)LQPETTDLY(23) binding stably to HLA molecules of the B62 type,

-(16)QPETTDLYCY(25) binding stably to HLA molecules of the A1 or B18 type.--

--12. (amended) Polyepitopic fragment of the E7 protein of HPV according to ~~one of claims~~claim ~~9 or 10~~, characterized in that it corresponds to the fragment of 17 amino acids delimited by the amino acids located in positions 44 and 60 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 16 as follows:

(44)QAEPDRAHYNIVTFCCK(60)

said fragment containing 4 epitopes binding stably to at least one of the 6 HLA molecules of the following types: A1, A3, A11, A29, B7, B18, B35, or B44, said epitopes being the following:

-(44)QAEPDRAHY(52) binding stably to HLA molecules of the A1 or B18 type,

-(45)AEPDRAHY(52) binding stably to HLA molecules of the A29 or B44 type,

-(46)EPDRAHYNIV(55) binding stably to HLA molecules of the B7 or B35 type,

-(53)NIVTFCCK(60) binding stably to HLA molecules of the A3 or A11 type.--

--13. (amended) Polyepitopic fragment of the E7 protein of HPV according to ~~one of claims~~claim 9 ~~or 10~~, characterized in that it corresponds to the fragment of 19 amino acids delimited by the amino acids located in positions 79 and 97 of the peptide sequence of the E7 protein of HPV, this latter fragment being characterized by the peptide sequence SEQ ID NO: 18 as follows:

(79)LEDLLMGTLGIVCPICSQK(97)

said fragment containing 4 epitopes binding stably to at least one of the 5 HLA molecules of the following types: A2, A3, A11, A29 or B44, said epitopes being the following:

-(79)LEDLLMGTL(87) binding stably to HLA molecules of the A29 or B44 type,

-(82)LLMGTLGIV(90) binding stably to HLA molecules of the A2 type,

-(86)TLGIVCPI(93) binding stably to HLA molecules of the A2 type,

-(89)IVCPICSQK(97) binding stably to HLA molecules of the A3 or A11 type.--

--14. (amended) Polyepitopic fragments of the E6 or E7 protein according to ~~one of claims~~claim 1 ~~to 13~~, characterized in that they correspond to the peptide sequences derived from the polyepitopic fragments defined in ~~one of claims 1 to 13~~claim 1, particularly:

- by substitution, and/or suppression, and/or addition of one or several amino acids, of the above-mentioned fragments, and/or

- by modification of at least one -CO-NH- peptide linkage of the peptide chain of the above-mentioned fragments, particularly by introduction of a retro or retro-inverso type linkage, and/or

- by substitution of at least one amino acid of the peptide chain of the sequence or of the above-mentioned fragment, with a non-proteinogenic amino acid,

said derived sequences containing peptides or pseudopeptides binding specifically to the same molecule or molecules of MCH as those binding to the peptides contained in the above-mentioned polyepitopic fragments from which they derive.--

--15. (amended) Nucleotide sequences coding for a polyepitopic fragment or for a peptide sequence derived according to ~~one of claims~~claim 1~~ to 14~~, said nucleotide sequences being derived from the sequence SEQ ID NO: 1 coding for the E6 protein, or from the sequence SEQ ID NO: 11 coding for the E7 protein.--

--16. (amended) Nucleotide sequences according to claim 15, selected from the following:

- the sequence SEQ ID NO: 3, coding for the polyepitopic fragment SEQ ID NO: 4~~ according to claim 5~~,

- the sequence SEQ ID NO: 5, coding for the polyepitopic fragment SEQ ID NO: ~~6 according to claim 6~~,

- the sequence SEQ ID NO: 7, coding for the polyepitopic fragment SEQ ID NO: 8~~ according to claim 7~~,

- the sequence SEQ ID NO: 9, coding for the polyepitopic fragment SEQ ID NO: 10~~ according to claim 8~~,

- the sequence SEQ ID NO: 13, coding for the polyepitopic fragment SEQ ID NO: 14~~ according to claim 11~~,

- the sequence SEQ ID NO: 15, coding for the polyepitopic fragment SEQ ID NO: 16~~ according to claim 12~~,

- the sequence SEQ ID NO: 17, coding for the polyepitopic fragment SEQ ID NO: 18~~ according to claim 13~~.--

--17. (amended) Polyclonal or monoclonal antibodies, directed against a polyepitopic fragment or against a peptide sequence derived according to ~~one of claims~~claim 1~~ to 14~~.--

--18. (amended) Lipopeptide characterized in that it comprises:

- a peptide portion comprising one or several polyepitopic protein fragments, or a peptide sequence derived from said fragments, as defined in ~~one of claims~~claim 1~~ to 14~~,

- and one or several lipophile portions, such as those comprising:

* a C4 to C20 hydrocarbon chain, saturated or unsaturated, linear or branched,

* or a steroid group, as the case may be bonded to the above-mentioned hydrocarbon chain,

said lipophilic portions being if desired associated with a short peptide vector comprising one or several ionized functions at physiological pH, and a function permitting the covalent bonding of said hydrocarbon chain and/or said steroid group.--

--19. (amended) Pharmaceutical composition, or vaccine, characterized in that it comprises:

~~*~~ - at least one polyepitopic fragment of the E6 or E7 protein of HPV, characterized in that they comprise a~~)~~

~~- at least one polyepitopic fragment of the E6 or E7 protein defined in one~~ peptide sequence of ~~claims 1~~about 15 to ~~13,~~

~~- and/or at least one peptide sequence derived from~~30 amino acids, this ~~fragment, as defined in claim 14,~~

~~- and/or at least one suitable vector, particularly lipopeptides according to claim 18 and/or micelles,~~peptide sequence containing ~~at least one above-mentioned polyepitopic fragment~~amino acid sequences of at least 3 different epitopes binding stably to HLA molecules of identical or different type, when these epitopes are obtained by enzymatic degradation of said peptide sequence, particularly in the ~~E6 or E7~~

~~proteinproteasome, and/orsuch that at least one above-mentioned sequence derived from these fragments,~~

~~in association with a physiologically acceptable vehicle,~~

~~said polyepitopic protein fragment and/or its derived sequence being, as the case may be, associated with one or several other exogenous epitopes recognized by auxiliary T cells, such as the peptide fragment delimited by the amino acids located in positions 830 and 846 of the peptide sequence of the tetanus toxin, hemagglutinin, or PADRE epitope,~~

~~* or b)~~

~~- at least one nucleotide sequence according~~4 HLA molecules of different types bind to these epitopes, these 4 HLA ~~15~~molecules being selected from among those of types A1, A2, A3, A11, A24, A29, B7, B8, B18, B27, B35, B44, B51 and B62,

- and/or at least one peptide sequence derived from this fragment, as defined in claim 14,

in association with a physiologically acceptable vehicle,

said polyepitopic protein fragment and/or its derived sequence being, as the case may be, associated with one ~~16, coding for an above-mentioned polyepitopic fragmentor~~ several other exogenous epitopes recognized by auxiliary T cells, ~~of~~ such as the ~~E6 or E7 protein,~~

~~- and/or at least one nucleotide sequence coding for a peptide sequence derived from this fragment, as defined above,~~

~~- and/or at least one above-mentioned suitable vector, selected particularly from the viruses, containing at least one above-mentioned nucleotide sequence,~~

~~-~~peptide fragment delimited by the amino acids located in ~~association with a physiologically acceptable vehicle,~~

~~* or c)~~

~~- antibodies according to claim 17, directed against a polyepitopic fragment of the E6 or E7 protein, and/or against a peptide sequence derived from these fragments~~ positions 830 and 846 of the peptide sequence of the tetanus toxin, hemagglutinin, ~~as defined above~~or PADRE epitope.

--20. (amended) The use of polyepitopic fragments of the E6 or E7 protein defined in ~~one of claims~~claim 1 ~~to 13, or the derived peptide sequences according to claim 14, or the nucleotide sequences according to claims 15 or 16, or of antibodies according to claim 17, or the lipopeptides according to claim 18~~, for the preparation of a medication or vaccine adapted for the prevention or treatment of pathologies connected with the infection of individuals by human papillomavirus, such as cervical intraepithelial neoplasias (CIN), invasive cancer of the neck of the uterus, vulvar intraepithelial neoplasias (VIN).--